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Physicochemical description of the absorption rate of a solute between water and 2,2,4-trimethylpentane

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Summary

The apparent rate of absorption, k_{app} , for steady-state flux of solutes of varying physicochemical character from an aqueous compartment (pH = 7), through a membrane filled with 2,2,4-trimethylpentane, to a 2,2,4-trimethylpentane sink compartment, can be given by a simple bilinear relation.

It is clearly demonstrated that experimentally, and in concordance with the theoretical model, a reduction in the aqueous diffusion layer thickness leads to a displacement of the bilinear $\log k_{app}$ versus $\log K_d$ curve both upwards and to the right. However, it can also be shown that at lower K_d values the interfacial transfer step can become rate limiting. In addition, there seems to be a linear relationship between the interfacial transfer rate constant and the $\log K_d$ value. This indicates that the simple bilinear model for describing the absorption rate has to be expanded to adequately describe drug rate of absorption.

Introduction

The systemic action of orally given drugs arises after their absorption through the gastrointestinal wall, with the extent and duration of their action partly depending upon their rate of absorption. Since there exists no clear relationship between drug structure and transport through biological (and artificial) membranes (Martin, 1981), examination of the absorption process can lead both to an improvement in

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the description of drug quantitative structure–activity relationships, and, in drug formulation, to an appreciation and possible manipulation of the important absorption step. In addition, many new dosage forms are being designed to include a transfer step through a rate-controlling membrane.

There have been several successful attempts to relate the *in vivo* absorption behaviour of a physicochemically closely related set of compounds to their physicochemical character (Seydel, 1983; Seydel and Schaper, 1982; Austel and Kutter, 1983). Such studies have clearly demonstrated that one of the most important terms in describing the absorption process is the distribution coefficient of the drug between an aqueous phase and a membrane phase. This characteristic of a solute is often modelled *in vitro* by the liquid/liquid distribution coefficient. The organic phase most used for determining the partition or distribution coefficient is octan-1-ol. Although the use of the octan-1-ol/water liquid/liquid distribution coefficient leads to good correlations in various structure/absorption relationships, in order to examine these relationships for a large number of solutes of widely differing physical and physicochemical structure, the *a priori* use of this solvent pair for appreciating the distribution process is not fully indicated, since transfer between water and octan-1-ol is due both to hydrophobic effects and specific solvation taking place in the oil.

We consider it more appropriate that studies be carried out first using a solvent pair in which only a single physicochemical effect occurs (Kinkel and Tomlinson, 1981). After this structure/absorption profile is known, other solvent pairs may be studied so that a more complete pattern of the effect of solvation on transfer can be obtained. Thus, this present contribution describes our studies on the extent and rate of transfer of 19 model solutes between water and 2,2,4-trimethylpentane (2,2,4-TMP). Future contributions will describe transfer rates between other solvent pairs, as well as *in vivo* rates of absorption.

Results found are examined within the framework of a (new) theoretical model of the rate of solute transfer between two immiscible phases. Further, since various theoretical models of absorption stress the importance of an aqueous diffusion layer in the absorption of drugs through membranes (Stehle and Higuchi, 1967; Stehle and Higuchi, 1972; Suzuki et al., 1970; Winne, 1978), we have used a rotating diffusion cell assembly (in which the diffusion layers can be accurately and precisely controlled), to measure flux through an artificial membrane.

Theory

The physical model used in the present study is given in Fig. 1. In such a system, where a sink condition is maintained in the acceptor phase, the pseudo steady-state flux may be given by:

$$J = \frac{-\left(\frac{dQ}{dt}\right)}{A} = -\frac{V_w(dC_w)}{A(dt)} = P_{\text{eff}} \cdot C_w \quad (1)$$

where J is the flux in $\text{mol} \cdot \text{s}^{-1} \cdot \text{cm}^{-2}$, Q is the amount of solute (moles), A is the area of membrane available for absorption (cm^2), V_w is the volume of the water phase (cm^3), P_{eff} is the effective permeability coefficient ($\text{cm} \cdot \text{s}^{-1}$) and C is the concentration of the solute in the donor water phase ($\text{mol} \cdot \text{cm}^{-3}$). The apparent rate constant (k_{app} ; s^{-1}) is calculated from:

$$k_{\text{app}} = \frac{A \cdot P_{\text{eff}}}{V_w} = - \frac{\ln\left(\frac{C_{w(t)}}{C_{w(0)}}\right)}{t} \quad (2)$$

where subscripts 0 and t refer to the initial state and the state at time t , respectively. For the model given in Fig. 1 and with the acceptor phase an oil, it can be shown (Zwolinsky et al., 1946; Albery et al., 1976; de Meere and Tomlinson, 1983) that:

$$k_{\text{app}}^{-1} = \frac{V_w}{A} \left(\frac{z_w}{D_w} + \frac{z_o}{K_d \cdot D_o} + \frac{1}{\alpha \lambda k_{\text{sm}}} + \frac{L}{\alpha \cdot D_o \cdot K_d} \right) \quad (3)$$

where D is the diffusion coefficient of the solute, with subscripts w and o referring to the water and organic phase, respectively, K_d is the distribution coefficient, (molar concentration scale), being equal to the ratio of the interfacial transfer rate from solution to membrane phase and vice versa, i.e. $K_{\text{sm}}/K_{\text{ms}}$, λ is the distance of one molecular step, L and α are the thickness and the porosity of the membrane, respectively, and z is the thickness of the diffusion layer.

For the case of a rotating diffusion cell, the diffusion layer thickness is described by (Levich, 1962):

$$z = 0.643 \nu^{1/6} \cdot D^{1/3} \cdot \omega^{-1/2} \quad (4)$$

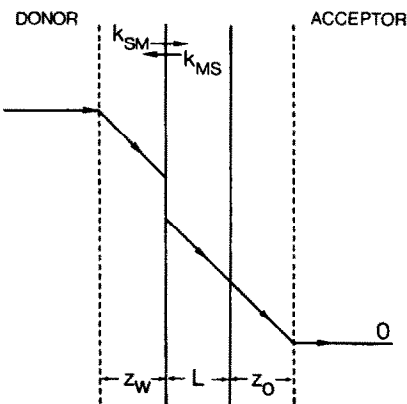


Fig. 1. Physical model showing the concentration gradient of a solute upon its diffusion from a donor aqueous phase through a diffusion layer of thickness z , a membrane (FHUP 04700, Millipore) filled with 2,2,4-trimethylpentane of thickness L and a 2,2,4-trimethylpentane diffusion layer of thickness z to sink acceptor phase of 2,2,4-trimethylpentane. k_{sm} and k_{ms} are the rate constants for interfacial transfer between the aqueous diffusion layer and the membrane phase.

where ν and ω are the kinematic viscosity ($\text{cm}^2 \cdot \text{s}^{-1}$) and the speed of rotation of the cell (Hz), respectively.

For the apparent rate constant in the water/oil/oil arrangement Eqn. 3 may be rearranged to:

$$k_{\text{app}}^{-1} = k_w^{-1} + k_{\text{sm}}'^{-1} + (K_d \cdot k_m)^{-1} + (K_d \cdot k_o)^{-1} \quad (5)$$

where subscript m refers to the membrane phase. From Eqn. 5 it can be seen that for solutes with a high K_d value, the apparent rate constant is determined principally by the rate of diffusion through the aqueous diffusion layer.

Eqn. 5 can be recast to give:

$$k_{\text{app}} = \frac{K_d \cdot k_m}{K_d \left(\frac{k_m}{k_w} + \frac{k_m}{k_{\text{sm}}'} \right) + 1 + \frac{k_m}{k_o}} \quad (6)$$

Since the organic phase in the membrane is similar to the organic phase behind the membrane, such that the diffusion coefficients in those phases are equal, Eqn. 6 may be developed to give:

$$\log k_{\text{app}} = \log K_d - \log(\beta \cdot K_d + X) + \log k_m \quad (7)$$

with $X = 1 + \alpha z_o/L$ and $\beta = (k_m/k_w + k_m/k_{\text{sm}}')$

This description of the water/oil/oil model is analogous (but not equal) to the one described by van der Waterbeemd et al. (1980) for the relationship between absorption rate and distribution coefficient. In the model of van der Waterbeemd et al. (1980), X equals unity; however, upon introducing a membrane phase into the model, X now deviates from unity. In addition, our model enables us to calculate the interfacial transfer rate from the intercept of a plot of k_{app}^{-1} versus $\omega^{-1/2}$. Further, whether the term β can be approximated by k_m/k_w or not, can be answered by studying the interfacial transfer term.

Eqn. 7, a familiar bilinear relationship, states that the plateau value of the $\log k_{\text{app}}$ versus $\log K_d$ plot can be approximated by $\log k_w$ (i.e. by assuming that the k_{sm}' term at high K_d values will be much greater than the k_w term).

It is also possible to calculate the $\log K_d$ at a point where the slope of the curve becomes less than a certain value. That is, since:

$$\frac{d \log k_{\text{app}}}{d \log K_d} = \frac{K_d \cdot dk_{\text{app}}}{k_{\text{app}} \cdot dK_d} \quad (8)$$

for the first derivative of Eqn. 7 (and by using Eqn. 6) we may write:

$$\frac{d \log k_{\text{app}}}{d \log K_d} = \frac{1}{\frac{\beta \cdot K_d}{X} + 1} \quad (9)$$

Thus, for example, the $\log K_d$ value at which the slope will be less than 10^{-2} can be approximated by:

$$\log K_d = 2 - \log \beta + \log X \quad (10)$$

This equation gives that the value of the $\log K_d$ on reaching the plateau of the $\log k_{app}$ versus $\log K_d$ plot, depends upon the ratio of the diffusion rate through the diffusion layers and the diffusion rate through the membrane. In addition, apart from an upwards shift of the $\log k_{app}$ versus $\log K_d$ curve upon a reduction in the aqueous diffusion layer thickness, this reduction will also be responsible for a shift of the curve to the right.

Fig. 2 gives the theoretical curves obtained using Eqn. 7 for different values of k_m and k_w , (with a small value of these indicating a large diffusion layer thickness or membrane thickness) and assuming the interfacial transfer term will be negligible. Furthermore, the curves shown have been obtained by varying z_o/L by the same amount as β , by assuming that the rotation speed will have nearly the same influence on k_w^{-1} as on z_o . The plateau value of each curve equals $\log k_w$.

It is also possible to derive equations for a water/oil/water system (i.e. the acceptor phase is an aqueous phase instead of an organic phase). This model might be more analogous to in vivo absorption.

For the water/oil/water mode, the apparent rate constant under steady-state conditions may be written as:

$$k_{app}^{-1} = \frac{V_{w1}}{A} \left(\frac{z_{w1}}{D_{w1}} + \frac{z_{w2}}{D_{w2}} + \frac{2}{\alpha \lambda k_{sm}} + \frac{L}{\alpha D_o K_d} \right) \quad (11)$$

where subscripts 1 and 2 refer to the aqueous phase in front of and behind the membrane, respectively. In a manner similar to that used to develop Eqn. 7, for the water/oil/water system we can derive from Eqn. 11 that:

$$\log k_{app} = \log K_d - \log(\beta \cdot K_d + 1) + \log k_m \quad (12)$$

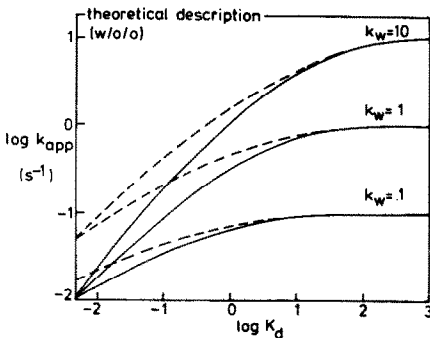


Fig. 2. Theoretical description of effect of solute K_d on membrane flux (water/oil/oil) obtained using Eqn. 7 for different values of k_m and k_w . Broken line: $k_m = 10 \text{ s}^{-1}$; solid line: $k_m = 1 \text{ s}^{-1}$.

where β is given by:

$$\beta = \frac{k_m(\zeta + 1)}{k_w} + \frac{2k_m}{k'_{sm}} \quad (13)$$

with ζ equal to the ratio of the diffusion layer thicknesses behind the membrane and in front of the membrane, i.e. z_2/z_1 .

For the case of a rotating diffusion cell, i.e. where ζ is unity, the plateau values of the $\log k_{app}$ versus $\log K_d$ curves are equal to $\log(k_w/2)$, so that the maximal value of $\log k_{app}$ in the w/o/w system will be a constant factor (i.e. $\log 2$) lower than the maximal values of $\log k_{app}$ in the w/o/o system. For the first derivative of Eqn. 12 it can be shown that:

$$\frac{d \log k_{app}}{d \log K_d} = \frac{1}{\beta \cdot K_d + 1} \quad (14)$$

which gives that the value of the $\log K_d$ at which the slope of $\log k_{app}$ versus $\log K_d$ plot becomes 10^{-2} can be approximated by:

$$\log K_d = 2 - \log \beta \quad (15)$$

This equation states that the shifts of the absorption rate curves of the water/oil/water model depend on the value of $\log \beta$, which is in contrast to that given for the water/oil/oil model (Eqn. 10).

The theoretical description of the effect of solute K_d on its membrane flux in the water/oil/water model is shown in Fig. 3, which has been constructed under the assumption that β can be approximately by $2(k_m/k_w)$.

The models, presented above, can be compared with other models, which have been described earlier.

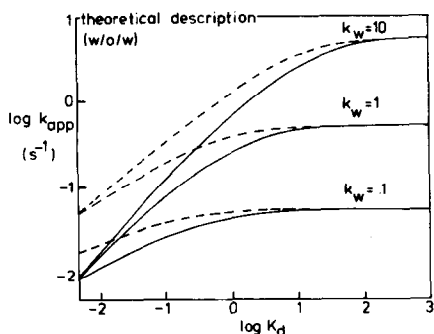


Fig. 3. Theoretical description of effect of solute K_d on membrane flux (water/oil/water) obtained using Eqn. 12 for different values of k_m and k_w . Broken line: $k_m = 10 \text{ s}^{-1}$; solid line: $k_m = 1 \text{ s}^{-1}$.

Several models exist for relating the biological response of a drug to its hydrophilic and lipophilic character. Most of these arise from kinetic or equilibrium considerations and lead to a parabolic or bilinear (hyperbolic) relationship.

The model most often used is that due to Hansch and Fujita (1968) who proposed that:

$$\log 1/C = -a(\log K_d)^2 + b \cdot \log K_d + c \quad (16)$$

where C is the effective concentration to obtain a certain response, K_d is the oil/water liquid/liquid distribution coefficient and a , b and c are system constants.

Considering the probability of a solute to reach a receptor, McFarland (1971) developed a bilinear relationship between $\log 1/C$ and $\log K_d$. This was later studied in more detail by Kubinyi (1977, 1978) and led to the following relationship being proposed:

$$\log 1/C = a \log K_d - b \cdot \log(\beta \cdot K_d + 1) + c \quad (17)$$

where the constant β depends upon the volume ratio between the lipoidal and the aqueous (bio)phases.

Other models, for example the Hyde model (Hyde, 1975; Hyde et al., 1979), lead to more or less similar results, with hardly an improvement in the predicting value of the behaviour of a solute *in vivo*, compared to the above models.

Since the distribution coefficient is the ratio of the rate constant of a solute from a water phase to an organic phase and vice versa, it becomes clear from the above models that the effect of a drug can depend upon its rate of absorption, with the corollary being that the measurable effect of a drug depends also on the time of measurement (Dearden and Townend, 1970).

Concerning absorption alone, Flynn and Yalkowsky (1972) have described the flux of a drug through a membrane by a bilinear relationship between the logarithm of the flux and the logarithm of the K_d value of a solute. The descending part of their model was explained by decreasing solubility of a drug with increasing distribution coefficient between an aqueous phase and an organic phase. However, since they examined the flux of a drug through a membrane, this latter effect will always be dependent upon the concentration of a drug.

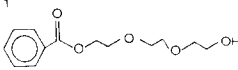
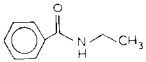
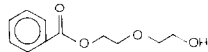
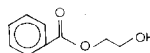
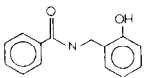



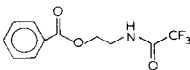


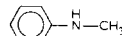
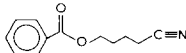
Since the flux at steady-state can be written as the concentration of a drug in a compartment multiplied by a constant, the dependency of this constant on the physicochemical properties of a solute needs to be studied, since its full appreciation would enable the flux to be described in terms of these physicochemical properties.

Van der Waterbeemd et al. (1980) have related the apparent rate constant of a solute from an aqueous phase to an organic phase (or vice versa) with the liquid/liquid distribution coefficient, using a bilinear relationship of a form similar to that described by Kubinyi (1977, 1978), i.e.

$$\log k_{w \rightarrow o} = \log K_d - \log(\beta \cdot K_d + 1) + c \quad (18)$$

TABLE 1


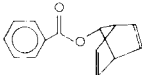
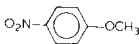
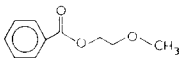
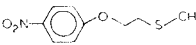
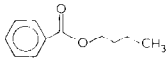
MEAN LOGARITHMS OF THE APPARENT RATE CONSTANTS, $\log \bar{k}_{app}$, AND THE VARIANCES OF THE MEAN OF DIFFERENT COMPOUNDS AT DIFFERING SPEEDS OF ROTATION, TOGETHER WITH THE LIQUID/LIQUID DISTRIBUTION COEFFICIENT, K_d , BE-

Compound	$\log K_d$	rotation speed in Hz					
		0.6600		1.3157		1.8518	
		$\log \bar{k}_{app}$	var. (10^{-3})	$\log \bar{k}_{app}$	var. (10^{-3})	$\log \bar{k}_{app}$	var. (10^{-3})
1 	-1.307	-5.571	3.000	-5.547	2.932	-5.785	3.020
2 	-1.103	-5.371	2.942	-5.361	2.462	-5.289	0.945
3 	-0.988	-5.697	3.010	-5.320	3.000	-5.396	3.110
4 	-0.979	-5.234	3.217	-5.006	3.032	-4.736	125.2
5 	-0.626	-4.983	0.046	-4.893	0.084	-4.889	0.134
6 	-0.448	-4.713	0.035	-4.615	0.040	-4.564	0.060
7 	-0.395	-4.653	0.338	-4.608	0.204	-4.554	0.005
8 	-0.110	-4.483	0.106	-4.410	0.087	-4.332	1.163
9 	0.060	-4.514	0.657	-4.438	0.667	-4.366	0.366
10 	0.340	-4.241	0.065	-4.132	0.126	-4.063	0.434
11 	0.479	-4.234	0.305	-4.091	0.004	-4.031	0.102
12 	1.030	-4.149	0.048	-4.002	0.011	-3.915	0.295
13 	1.032	-4.194	1.319	-4.037	2.889	-3.970	0.049

TWEEN WATER (pH = 7, IONIC STRENGTH = 0.01 mol·dm⁻³) AND 2,2,4-TRIMETHYLPENTANE

2.4509		2.9154		3.4965		4.8309		8.0645	
log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)
-5.577	3.100	-5.611	3.000	-5.524	3.090	-5.634	2.880	-5.706	3.120
-5.390	2.851	-5.306	5.215	-5.376	2.783	-5.421	1.918	-5.422	2.058
-5.189	2.950	-5.186	3.440	-5.162	2.890	-5.181	2.750	-5.130	3.330
-5.052	1.252	-5.053	1.029	-5.066	1.021	-5.077	0.447	-5.013	19.11
-4.828	0.011	-4.860	0.015	-4.832	0.206	-4.762	0.041	-4.787	0.003
-4.562	0.524	-4.518	0.027	-4.516	0.124	-4.499	0.182	-4.458	0.098
-4.516	0.148	-4.496	0.003	-4.486	0.097	-4.440	0.097	-4.441	0.086
-4.290	1.811	-4.263	0.611	-4.243	0.809	-4.213	0.689	-4.152	0.617
-4.332	1.294	-4.312	0.486	-4.319	0.038	-4.268	0.267	-4.249	0.038
-4.025	0.443	-3.986	0.077	-3.960	0.017	-3.913	0.07	-3.842	0.019
-3.965	0.009	-3.924	0.103	-3.898	0.008	-3.851	0.014	-3.762	0.086
-3.857	0.378	-3.827	0.868	-3.779	0.073	-3.721	0.115	-3.633	0.347
-3.884	1.219	-3.832	3.235	-3.828	1.360	-3.772	0.908	-3.675	0.944

TABLE 1 continued

Compound	$\log K_d$	rotation speed in Hz					
		0.6600		1.3157		1.8518	
		$\log \bar{k}_{app}$	var. (10^{-3})	$\log \bar{k}_{app}$	var. (10^{-3})	$\log \bar{k}_{app}$	var. (10^{-3})
14 	1.052	-4.163	0.543	-4.008	0.634	-3.934	0.917
15 	1.251	-4.221	0.500	-4.055	0.540	-3.965	0.495
16 	1.317	-4.111	0.025	-3.968	0.035	-3.868	0.015
17 	1.339	-4.212	0.032	-4.046	0.068	-3.939	0.116
	1.846	-4.203	0.327	-4.031	0.063	-3.938	0.020
19 	2.335	-4.131	0.011	-3.967	0.950	-3.931	0.164

In this model, the c constant correlates with the diffusion rate constant for transport through the organic diffusion layer, and the β constant correlates with the ratio of the rate of diffusion through the organic diffusion layer and the rate of diffusion through the aqueous diffusion layer. This is contrary to the Kubinyi model, where the constants correlate to volume ratios. Van der Waterbeemd et al. (1980) have shown that their model can be used to study the absorption rate behaviour of a set of structurally similar compounds.

The model proposed in this present study has been developed from the findings of van der Waterbeemd et al. (1980); however, here we have studied a heterogeneous set of compounds, and examine in some detail the influence of the diffusion layer thickness on the nature of the relationship between the logarithm of the K_d value of a solute and the logarithm of the apparent rate constant, by incorporating a support membrane into the two-phase system. Also, the influence of interfacial transfer on the absorption process (a factor which has been completely ignored by most workers), has been determined by us.

Experimental

Materials

The compounds used in this study are listed in Table 1. Compounds 6, 7, 8, 10, 11 and 13 are from Fluka (Hicol, Rotterdam, The Netherlands), compounds 2 and 15

2.4509		2.9154		3.4965		4.8309		8.0645	
log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)	log \bar{k}_{app}	var. (10 ⁻³)
-3.877	0.916	-3.850	0.988	-3.814	0.706	-3.744	1.218	-3.666	3.597
-3.937	0.620	-3.843	0.560	-3.809	0.478	-3.809	0.545	-3.709	0.610
-3.815	0.089	-3.781	0.077	-3.736	0.054	-3.689	0.112	-3.592	0.390
-3.868	0.228	-3.827	0.036	-3.781	0.002	-3.731	0.002	-3.647	0.034
-3.898	0.099	-3.876	0.132	-3.806	0.011	-3.756	0.089	-3.674	0.026
-3.889	0.666	-3.782	0.137	-3.735	0.059	-3.736	0.210	-3.649	0.174

from Pfaltz and Bauer (Rijnland Industrie en Handelsmij., Capelle a/d IJssel, The Netherlands), compound 19 from Kodak Eastman (Tramedico, Weesp, The Netherlands), compound 14 from Alfa (Hicol, Rotterdam, The Netherlands) and compounds 1, 3, 4, 5, 9, 12, 17 and 18 have been supplied by ICI (Macclesfield, Cheshire, U.K.). The compounds have been chosen so as to represent a wide range of physicochemical properties. All these compounds have been used as received, except for aniline, which was distilled under vacuum before use.

All buffer components (analytical grade) and 2,2,4-trimethylpentane (analytical grade) were from Merck (Amsterdam, The Netherlands).

Water was freshly distilled using an all-glass still after deionization over a mixed-bed ion exchanger. The buffer used was a phosphate buffer (pH = 7) having an ionic strength of 0.01 mol · dm⁻³ (Christian et al., 1962). Both aqueous and organic phase were presaturated with each other at the temperature of the experiment. Depending on the molar extinction coefficient of a solute, the concentration of the solution was usually in the order of 10⁻⁴ mol · dm⁻³.

Methods

A rotating diffusion cell similar to that described in the literature (Albery et al., 1976; de Meere and Tomlinson, 1983), and modified to have an adjustable membrane-holder, has been used to measure the rate of transport of a solute from an aqueous buffer to 2,2,4-trimethylpentane at 298.2K. The aqueous donor phase (44 cm³) and organic acceptor phase (320 cm³) were separated by a porous polytetraflu-

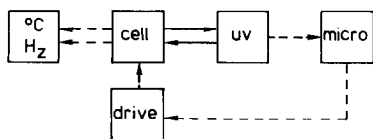


Fig. 4. Rotating diffusion cell set-up. Dashed lines indicates an information or command link.

oroethylene membrane (Millipore, type FHUP04700, 0.5 μm pore size; 60 μm thick; porosity 0.85) saturated with 2,2,4-trimethylpentane. To maintain a sink condition the acceptor phase was constantly replenished with 2,2,4-TMP. A scheme of the assembly, different from our previously reported arrangement (de Meere and Tomlinson, 1983), is given in Fig. 4. An APPLE II PLUS microcomputer controlled the speed of the diffusion cell drive motor (Neckar motor, kg662/z6/1221614 fitted with a tachometer; Elmekanic, Hilversum, The Netherlands) by means of connecting the four annunciator outputs of the microcomputer with several resistances, which regulated the voltage to the motor. The rotation speed of the cell was varied from 0.66 to 8.06 Hz.

The rotation speed of the cell was monitored using a digital counter (Venner digital counter, type TSA 6634a), and was found to vary by no more than 1% during an experiment.

The donor phase was pumped through a spectrophotometer using a high pressure pump (Orlita, type DMP, 1515). All tubing was made of narrow-bore stainless steel, and was isolated to avoid fluctuations in the temperature of the pumped phase. Temperature was maintained at $298.2 \pm 0.5\text{K}$ using a water bath and circulator.

The rate of transport of a solute from the aqueous donor phase to the organic acceptor phase was constantly followed at the wavelength of maximum ultraviolet absorbance using a Pye-Unicam SP8-100 UV/VIS spectrophotometer. Over the concentration range studied each solute obeyed the Beer-Lambert law, enabling the rate constant to be calculated directly from the \ln absorbance versus time profile. The rate of transport at every rotation speed was calculated using linear regression by an APPLE II PLUS computer interfaced with the spectrophotometer.

The time to reach a pseudo steady-state was found to vary between 2 and 9 h depending upon the compound being studied. The experimental results were fitted to our model using a mainframe computing and a minimization algorithm of Marquardt (1963).

The distribution coefficient of every solute between the aqueous buffer phase and 2,2,4-trimethylpentane was determined by a shake-flask method at 298.2K in triplicate (Table 1).

Results and Discussion

The experimentally measured absorption rates of 19 compounds at eight different rotation speeds of the cell in the water/oil/oil system, together with the calculated

variances of the mean, are shown in Table 1. Each value given is the mean of between 2-5 readings. Also given are the measured distribution coefficients of the compounds between water (pH = 7) and 2,2,4-trimethylpentane. Figure 5 gives the experimental results obtained at the two extreme rotation speeds. It is clear that the experimental $\log k_{app}$ versus $\log K_d$ data have profiles which resemble that of the theoretical curves for the water/oil/oil model shown in Fig. 2. In order to fit the data points to Eqn. 7 some estimations of the parameters making up the value of X must be made. From the dynamic viscosity of 2,2,4-TMP at 298.2K of 0.447cP (Landolt-Bornstein, 1969) and a density at 298.2K of $0.688\text{g} \cdot \text{cm}^{-3}$ (Landolt-Bornstein, 1974) a kinematic viscosity of 2,2,4-TMP at 298.2K of $\nu = 732.10^{-2}\text{cm}^2 \cdot \text{s}^{-1}$ can be calculated.

Assuming the diffusion coefficient of a solute in 2,2,4-TMP to be nearly equal to the diffusion coefficient of self-diffusion (Flynn et al., 1974), i.e. $D_{25} = 2.75 \cdot 10^{-5}\text{cm}^2 \cdot \text{s}^{-1}$ for 2,2,4-TMP (Landolt-Bornstein, 1969), we can estimate the values of z_0 in the formula of X from Eqn. 4. To obtain the effectual α correction term in the estimation of the value of X, we have performed an experiment to measure the diffusion rate from an inner compartment filled with 2,2,4-TMP through the membrane to an outer compartment of 2,2,4-TMP (volume of the outer compartment being 1dm^3), i.e. a oil/oil system. From this, we may calculate the diffusion coefficient of a solute in 2,2,4-TMP from the slope term in the relation between k_{app}^{-1} versus $\omega^{-1/2}$; i.e. using

$$k_{app}^{-1} = \frac{V_w}{A} \left(2 \times 0.643 \nu^{1/6} D_o^{-2/3} \omega^{-1/2} + \frac{L}{\alpha D_o} \right) \quad (19)$$

which can be simplified to give:

$$k_{app}^{-1} = B' \cdot \omega^{-1/2} + C' \quad (20)$$

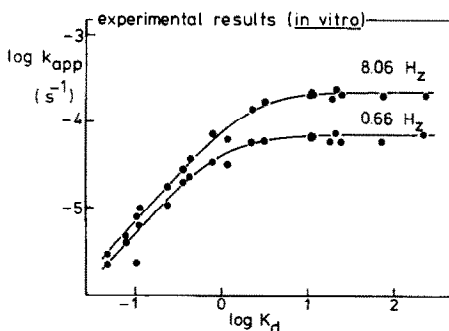


Fig. 5. The measured logarithm of the apparent rate constant for a number of aromatic solutes of varying physicochemical character against the measured logarithm of the distribution coefficient between pH 7 phosphate buffer ($0.01\text{mol} \cdot \text{dm}^{-3}$) and 2,2,4-trimethylpentane at two different rotation speeds at 298.2K.

Since there is neither an interfacial nor a K_d term in the intercept value of the above equation, from the calculated diffusion coefficient and the thickness of the membrane ($60 \cdot 10^{-6}$ m), the effectual porosity α of Eqn. 3 and Eqn. 7 can be calculated. Results so obtained are given in Table 2. The mean value of $\alpha = 0.67$ has been used to calculate the estimate of X. As may be seen from Table 2, the found diffusion coefficients of the compounds examined deviate little from the diffusion coefficient of self-diffusion used in the approximation of X. The estimates of the values of X at different rotation speeds of the cell are shown in Table 3, and have been used to fit the experimental $\log k_{app}$ and $\log K_d$ values at a certain rotation speed to the bilinear model given by Eqn. 7. The experimental variances of the mean of the $\log k_{app}$ are used as weighting factors in the weighted least-squares analysis (Drapper and Smith, 1966). The found values of k_m and k_w at fixed speeds of rotation, together with the appropriate statistics are given in Table 4. From this it can be seen that the experimental data fits with the bilinear model of Eqn. 7 quite well, with the average relative standard deviation of the estimated values being less than 10%. By

TABLE 2

CALCULATED DIFFUSION COEFFICIENTS OF SOME COMPOUNDS IN 2,2,4-TRIMETHYLPENTANE AND THE α TERM OF EQN. 7 USING THE k_{app}^{-1} VERSUS $\omega^{-1/2}$ RELATION

Compound	Regression coefficients			D_o ($10^{-5} \text{ cm}^2 \cdot \text{s}^{-1}$)	α	k_m^a (10^{-4} s^{-1})
	B' ($\text{s}^{1/2}$)	C' (s)	r ($n = 8$)			
aniline	10,283	5417	0.999	2.736	0.6669	1.860
<i>p</i> -chloro- aniline	10,942	6012	0.998	2.493	0.6569	1.663
nitroanisole	11,234	5971	0.990	2.396	0.6909	1.673

^a Calculated from $k_m = 1/C'$.

TABLE 3

ESTIMATIONS OF THE VALUE OF X^a AT DIFFERENT ROTATION SPEEDS OF THE CELL USED

Rotation speed, ω (Hz)	X
0.6600	2.1718
1.3157	1.8344
1.8518	1.7033
2.4509	1.6114
2.9154	1.5571
3.4965	1.5119
4.8309	1.4355
8.0645	1.3370

^a Where $X = 1 + \frac{0.643\nu^{1/6} \cdot D_o^{1/3} \cdot \omega^{-1/2} \cdot \alpha}{L}$

assuming an average diffusion coefficient of a solute in water of $1.10^{-5} \text{ cm}^2 \cdot \text{s}^{-1}$, we can see from Table 4 that the expected k_w value does not deviate much from the found k_w value. Since k_w is proportional to ω , then $k_w = E \cdot \omega^{1/2}$. We can calculate the value of the proportionality constant E for every rotation speed. The mean E constant has been calculated to be $9.82 \cdot 10^{-5} (\pm 6.72 \cdot 10^{-7}) \text{ s}^{-1/2}$. This value of E enables us to rewrite Eqn. 7 to give an equation in which k_w is a constant depending only upon the speed of rotation.

Hence, the found values of k_m can now be compared with the values of C in Table 2 in the oil/oil/oil model, since by definition $k_m = 1/C$. Comparison of the values of k_m given in Table 4 with those given in Table 2, shows that the use of the minimization algorithm results in a slightly different result than that found with the oil/oil/oil experiments. In particular, the calculated k_m value deviates from the experimental determined k_m values most at the highest speed of stirring (which could be due to either a loss in sink conditions or possible mass flow through the membrane).

The k_m values in Table 4 are estimations made from only 19 data points. It is also possible to make an estimation of k_m from all available data points ($n = 152$) and at the same time to study the influence of the interfacial transfer rate on the absorption process.

For all compounds studied we have measured the absorption rates at 8 different rotation speeds from which the intercept term in the k_{app}^{-1} versus $\omega^{-1/2}$ can be calculated.

Since the intercept term in the water/oil/oil system is defined as:

$$C' = \frac{LV_w}{\alpha K_d \cdot D_o \cdot A} + \frac{1}{k'_{sm}} \quad (21)$$

TABLE 4

RATE CONSTANT^a ESTIMATIONS AND THEIR STANDARD ERRORS AT DIFFERING SPEEDS OF ROTATION OBTAINED BY WEIGHTED LEAST-SQUARES REGRESSION ANALYSIS

Rotation speed (Hz)	k_m	S.E.	k_w	S.E.	k_w^b
0.6600	1.3844	0.1006	0.7584	0.0353	0.7809
1.3157	1.5085	0.0992	1.1373	0.0367	1.1025
1.8518	1.4829	0.0563	1.3050	0.0483	1.3080
2.4509	1.1877	0.0571	1.7784	0.1110	1.5047
2.9154	1.4133	0.0690	1.7076	0.1720	1.6411
3.4965	1.4860	0.1425	1.8035	0.0615	1.7972
4.8309	1.5693	0.1194	2.0713	0.0666	2.1126
8.0645	1.0343	0.0485	2.6392	0.2574	2.7295

^a All values have been multiplied by 10^4 and have units of s^{-1} , and are as defined in text.

^b Calculated k_w values by assuming a diffusion coefficient of a solute in water of $1 \cdot 10^{-5} \text{ cm}^2 \cdot \text{s}^{-1}$.

with $k'_{sm} = V_w/A \cdot \alpha \lambda k_{sm}$, then by knowing the K_d value, estimation of $L \cdot V_w / \alpha \cdot D_o \cdot A$, (i.e. k_m^{-1}) enables us to calculate the k'_{sm} term for every compound. However, the interfacial transfer can only be calculated in a certain region of the $\log k_{app}$ versus $\log K_d$ curve, since at low values of $\log K_d$ the experimental data points are not precise enough to draw any significant conclusions. In this region of low K_d values the aqueous diffusion layer thickness has hardly any influence on the observed (slow) absorption rates; similarly, at high K_d values the intercept terms become very low and in the same order as the standard error. The observed meaningful relationships between k_{app}^{-1} and $\omega^{-1/2}$ from which we can calculate an interfacial transfer term are given in Table 5.

It is possible to relate the observed $\log k'_{sm}$ values linearly with the $\log K_d$ values for a small number of compounds. The observed relationship being:

$$\log k'_{sm} = 1.7904 \log K_d - 2.984 \quad r = 0.797, n = 6 \quad (22)$$

If compound 9 is considered as an outlier, perhaps due to a different diffusion coefficient in water or 2,2,4-TMP compared to the estimated values, its omission leads to the observed relationship becoming much more significant, i.e.

$$\log k'_{sm} = 2.2619 \log K_d - 2.693 \quad r = 0.975, n = 5$$

This linear relationship between $\log k'_{sm}$ and $\log K_d$ means that at lower values of K_d , the value of k'_{sm} may become in the same order of magnitude as, or even lower than the value of k_w . Therefore, the assumption made, that β can be approximated by k_m/k_w by ignoring k'_{sm} , will not hold at lower K_d values.

If we assume that there exists a linearity between $\log k'_{sm}$ and $\log K_d$ with 2,2,4-TMP as the organic phase; i.e.

$$\log k = m \log K - c \quad (24)$$

TABLE 5

SLOPE (B') AND INTERCEPT (C') REGRESSION COEFFICIENTS FOR THE RELATIONSHIP BETWEEN k_{app}^{-1} and $\omega^{-1/2}$ WITH THEIR STANDARD ERRORS, AND THE CALCULATED APPARENT INTERFACIAL TRANSFER RATE CONSTANTS, k'_{sm}

Compound no.	$\log K_d$	Regression coefficients						$\log k'_{sm}^a$ (s^{-1})
		B' ($s^{1/2}$)	S.E.	C' (s)	S.E.	n	r	
5	-0.626	41,357	3578	44,547	2589	19	0.962	-4.305
6	-0.448	25,853	1412	19,126	1020	23	0.970	-3.476
7	-0.395	21,671	1567	19,392	1155	15	0.968	-3.708
8	-0.110	19,143	1381	7537	999	16	0.965	-2.747
9	0.060	18,155	1552	10,588	1097	21	0.937	-3.746
10	0.340	12,070	538	2739	389	16	0.986	-2.041

^a Calculated from $C' - (K_d \cdot k_m)^{-1}$, with the mean value of $k_m^{-1} = 5752$.

then by introducing this into the β term, leads to Eqn. 7 being rewritten to give:

$$\log k_{\text{app}} = \log K_d - \log\left(\left(k_m/k_w + k_m/(K_d^m \cdot 10^c)\right)K_d + X\right) + \log k_m \quad (25)$$

All the data used for estimating the values of the above unknown parameters have been checked using the minimization program by first rewriting k_w as $k_w = E \cdot \omega^{1/2}$ and then fitting the data to the following expression, i.e.

$$\log k_{\text{app}} = \log K_d - \log\left(\left(k_m/(E \cdot \omega^{1/2}) + k_m/(K_d^m \cdot d)\right)K_d + X\right) + \log k_m \quad (26)$$

The final results of the weighted least-squares analysis are shown in Table 6. Here it is seen that the value of K_m has a relative standard error of less than 10%, and now more resembles the value found using the oil/oil/oil system. Furthermore, the values of $m = 1.796$ and $c = \log d = -3.253$, found with the minimization algorithm, are nearly equal to those found in a completely different manner, i.e. by studying the interfacial transfer rate from the intercept terms in the k_{app}^{-1} versus $\omega^{-1/2}$ relationships (see Eqn. 22). Although the statistics of m and d (or c) in Table 6 are poor, the fact that similar absolute values are obtained by two independent and different approaches, appears to enhance their significance.

Upon ignoring an interfacial transfer step, i.e. by reducing β to k_m/k_w , all the data points can be fitted quite well with only two parameters, i.e. k_m and E . The standard errors of these are small, although the total residual sum of squares is nearly twice as high as when an interfacial transfer term is introduced into the model.

In this present study it has not been possible to determine the absolute values of m and c . This is in part due to the uncertainty in the magnitude of the value of k_m . However, both the reduction of the total residual sum of squares by nearly a factor of two caused by introducing the m and c parameters into the model, and the resemblance of the values obtained with both methods, appear to indicate that the introduction of a K_d -dependent k'_{sm} value into the β term of the bilinear relationship between the $\log k_{\text{app}}$ and the $\log K_d$ (i.e. Eqn. 25) is a valid one. The significance of the value of m (i.e. the dependency of the k'_{sm} value upon the K_d value), and the value of c (i.e. an apparently system-dependent parameter), have to be studied in

TABLE 6

ESTIMATION OF THE PARAMETERS OF EQN. 26 AND THEIR STANDARD ERRORS BY WEIGHTED LEAST-SQUARES REGRESSION ANALYSIS ($n = 152$)

R.S.S. ^a (10^4)	k_m (10^{-4} s^{-1})	S.E.	m	S.E.	d (10^{-4} s^{-1})	S.E.	E ($10^{-4} \text{ s}^{-1/2}$)	S.E.
0.8357	1.9847	0.1879	1.796	0.193	5.583	2.182	0.9820 ^b	
1.5256	1.2925	0.0293	—		—		0.9895	0.0191

^a Total residual sum of squares

^b Taken as a constant

more detail, and will be concentrated upon in our further studies where organic phases other than 2,2,4-TMP will be employed in the study of the absorption process.

Conclusions

In this study we have examined the influence of some physicochemical parameters on the steady-state absorption rate of a heterogeneous set of compounds from water to an organic phase, i.e. 2,2,4-TMP, through a membrane saturated with that organic phase. A pseudo steady-state flux has been obtained by maintaining sink conditions in the acceptor phase. The time to reach a steady-state flux was found to vary between 2 and 9 h depending upon the compound studied.

The water/oil/oil model enables us to examine one part of the absorption process. Mathematically it can be shown that the equations derived for a water/oil/oil model are comparable to the equations derived for the water/oil/water model.

As a first approximation, a bilinear equation relating the logarithm of the absorption rate and the logarithm of the distribution coefficient between an aqueous phase and an organic phase can be derived. The form of the equation (Eqn. 7) resembles, but is not equal to, the bilinear equations describing biological activity or absorption rates published previously.

The equation derived by us states that a reduction in the aqueous diffusion layer thickness, i.e. an increase in the k_w value, leads to a shift upwards of the $\log k_{app}$ versus $\log K_d$ curve, whereby the maximal value of the $\log k_{app}$ in the water/oil/oil model is equal to the $\log k_w$ value. Furthermore, a reduction in the aqueous diffusion layer thickness leads to a shift to the right of the $\log k_{app}$ versus $\log K_d$ value, which is dependent upon the ratio of the diffusion rate through the diffusion layers and the diffusion rate through the membrane. These theoretical considerations have been confirmed experimentally by this study.

A deviation from the bilinear relationship stated by Eqn. 7, and where the interfacial transfer rate is ignored at first, will occur at lower K_d values. In that case the value of the interfacial transfer rate becomes of the same order of magnitude as the k_w value. This means that an interfacial transfer term has to be introduced into the bilinear model.

Although the interfacial transfer is difficult to study, it is possible to make some assumptions which permit an estimation of the value of the interfacial transfer rate to be made from the intercept in the linear relation between k_{app}^{-1} and $\omega^{-1/2}$. Experiments appear to indicate that there is a linear relationship between the $\log k'_{sm}$ and the $\log K_d$ value. There is some doubt about the absolute value of the slope and the intercept term of that relationship. However, introducing a linear relationship between the $\log k'_{sm}$ and the $\log K_d$ into the β term of Eqn. 7 and using the minimization algorithm of Marquardt on all of the data points leads to nearly the same values of the slope and the intercept term of the new function being found. This indicates that the extension of the simple bilinear model of drug absorption

with an interfacial transfer rate term, which is also dependent upon the K_d value, is a valid one. The physicochemical meaning of these newly introduced parameters, which might be system-dependent, are to be studied further by us.

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